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REVIEW ARTICLE

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Long noncoding RNA and its contribution to autism spectrum disorders

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Summary

Recent studies have indicated that long noncoding RNAs (lncRNAs) play important roles in multiple processes, such as epigenetic regulation, gene expression regulation, development, nutrition-related and other diseases, toxic response, and response to drugs. Although the functional roles and mechanisms of several lncRNAs have been discovered, a better understanding of the vast majority of lncRNAs remains elusive. To understand the functional roles and mechanisms of lncRNAs is critical because these transcripts represent the majority of the transcriptional output of the mammalian genome. Recent studies have also suggested that lncRNAs are more abundant in the human brain and are involved in neurodevelopment and neurodevelopmental disorders, including autism spectrum disorders (ASDs). In this study, we review several known functions of lncRNAs and the potential contribution of lncRNAs to ASDs and to other genetic syndromes that have a similar clinical presentation to ASDs, such as fragile X syndrome and Rett syndrome.

KEYWORDS
Angelman syndrome, autism spectrum disorders, down syndrome, long noncoding RNA, neurodevelopment, Prader-Willi syndrome, Rett syndrome

1 | INTRODUCTION

Autism spectrum disorders (ASDs) are a group of common neurodevelopmental disorders characterized by impaired reciprocal social interaction and communication and restricted and repetitive behavior or interests. The classification of ASDs has been deemphasized in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) because of the heterogeneity of both clinical features and pathogenesis.[1] Over the past 40 years, the reported prevalence of ASDs has showed regional differences but has been steadily increasing worldwide.[2] ASDs have a reported prevalence of 1.47% in the United States and 2.64% in Korea, and an estimated prevalence of 0.25% in China.[3-5] However, therapeutic strategies for most patients with ASDs are insufficient.

The etiologies of ASDs are complex and not well understand to date. Genetic and environmental factors, both alone and in

combination, have been implicated in the pathogenesis of ASDs.[6-10] Mutations in many genes, including neuroligin-3 (NLGN3), neuroligin-4 (NLGN4), neurexin-1 (NRXN1), SH3 and multiple ankyrin repeat domains protein 2 (SHANK2), SH3 and multiple ankyrin repeat domains protein 3 (SHANK3), Parkinson protein 2 (PARK2), MACRO domain containing 2 (MACROD2), and semaphorin-5A (SEMA5A), have been associated with ASDs.[6,7,10] Several human syndromes derived from a single gene mutation, including fragile X syndrome (FXS), Rett syndrome (RTT), and Prader-Willi syndrome (PWS), increase the risk of ASDs (a phenomenon discussed further in "LncRNAs and the risk of ASDs" below). The autism database AutDB is a publicly available genetic database for ASDs and includes all genes that have been implicated in ASDs (http://www.mindspec.org/autdb.html). As of the end of June, 2015, this database had collected 740 genes associated with ASDs. Notably, most of those genes are candidate genes, and their association with ASDs has not been demonstrated by replication or by functional studies. The environment may also play a role, as infection, inflammation and metabolic factors are also reported to have associations with ASDs.[8,9]

Epigenetic modifications also contribute to the etiology of ASDs. For example, Wang et al.[11] reported that hypermethylation of the enolase 2 (ENO2) gene is present in 15% of patients with ASDs. It is noteworthy that microRNAs (miRNAs) and long noncoding RNAs (lncRNAs), which play important roles as transcriptional and/or post-transcriptional regulators,[12-20] have also been implicated in ASDs and other neurological disorders. Some prominent functional studies have shown that lncRNAs perform a wide variety of functions, including participating in the recruitment of chromatin modifying complexes, providing a scaffold for the assembly of protein complexes, modulating alternative splicing, and employing enhancer-like functions.[12,21,22] These diverse functions are essential components of both the normal physiological and developmental processes, as well as the etiology of many disorders and complex diseases.[23-25] Currently, full and systematic discussions of the relationship between lncRNAs and ASDs are highly limited. Therefore, this review summarizes the available information from previous outstanding publications with a focus on the contribution of lncRNAs to ASDs and to other genetic syndromes, such as FXS and RTT, which have a similar clinical presentation to ASDs.

2 | LNCRNAS AND THEIR MECHANISMS OF ACTION

LncRNAs, which are defined as untranslated RNA molecules greater than 200 nucleotides in length, can be derived from sense or antisense strands within protein-coding genes, intergenic regions, or pseudogenes. LncRNAs are spliced and processed so that they include a 5′-methyl-guanosine cap and 3′-poly (A) tail once transcribed. LncRNAs can be localized to the nucleus or the cytoplasm, but many lncRNAs are expressed with temporal and tissue and/or cell specificity.[24] LncRNAs have a poorly conserved primary structure but relatively well-conserved secondary structure and splicing.[26,27] The mechanisms of action of lncRNAs are diverse and not yet fully understand, but mainly include genetic imprinting, chromatin remodeling, cell cycle regulation, splicing regulation, mRNA degradation and translation regulation.[28,29] LncRNAs have been shown to control every level of the regulation of the gene expression pathway.[24] An overview of the cellular functions of lncRNAs is shown in Figure 1. This diverse set of functions and complex mechanisms further emphasizes the idea that lncRNAs are key components of numerous cellular processes. Generally, lncRNAs regulate gene expression at three levels: transcriptional regulation, posttranscriptional regulation and epigenetic regulation.[30]

2.1 | LncRNAs regulate the transcription of other genes

Transcriptional regulation is the most vital regulation of gene expression in both eukaryotes and prokaryotes. LncRNAs can regulate the transcription of other genes in several ways: by regulating the combination and assembly of transcription factors,[31] by forming a three-stranded complex with a regulatory sequence,[32] by regulating RNA polymerase II, and by transcriptional interference.[33,34] For example, transcriptional interference which refers to transcription of lncRNAs from alternative transcription start sites in the vicinity of another gene, which may interfere with the transcription of that gene regulates key developmental pathways.[35,36]

2.2 | LncRNAs regulate RNA processing and translation

LncRNAs play a role not only in transcriptional regulation but also in posttranscriptional regulation. They can regulate pre-mRNA splicing through the isolation of splicing factors or by regulating the distribution and phosphorylation of splicing factors in splicing speckles.[37,38] Bernard et al.[39] showed that metastasis associated lung adenocarcinoma transcript 1 (MALAT1) is highly expressed in neurons and impacts the expression of genes related to synaptogenesis by regulating the serine/arginine splicing factor. LncRNAs can also regulate RNA transfer, translation and degradation. In a typical example, the BACE1-antisense transcript (BACE-AS) is the natural antisense transcript of the β-site APP cleaving enzyme 1 gene (β-secretase 1, BACE1). BACE1 protein expression will increase if BACE1-AS binds to the BACE1 mRNA. The BACE1 protein can later cleave the β-amyloid peptide precursor to produce more β-amyloid peptide.[40] High levels of β-amyloid peptide plaques in the brain are a prominent feature of Alzheimer's disease.[41] Thus, BACE-AS participates in the pathological process of Alzheimer's disease.[40]

2.3 | LncRNAs participate in epigenetic regulation

Epigenetic regulation results in a change in gene expression without changing the nucleotide sequence of the gene. Common epigenetic phenomena include DNA methylation, gene silencing, histone modification, genomic imprinting and RNA editing. LncRNAs have received

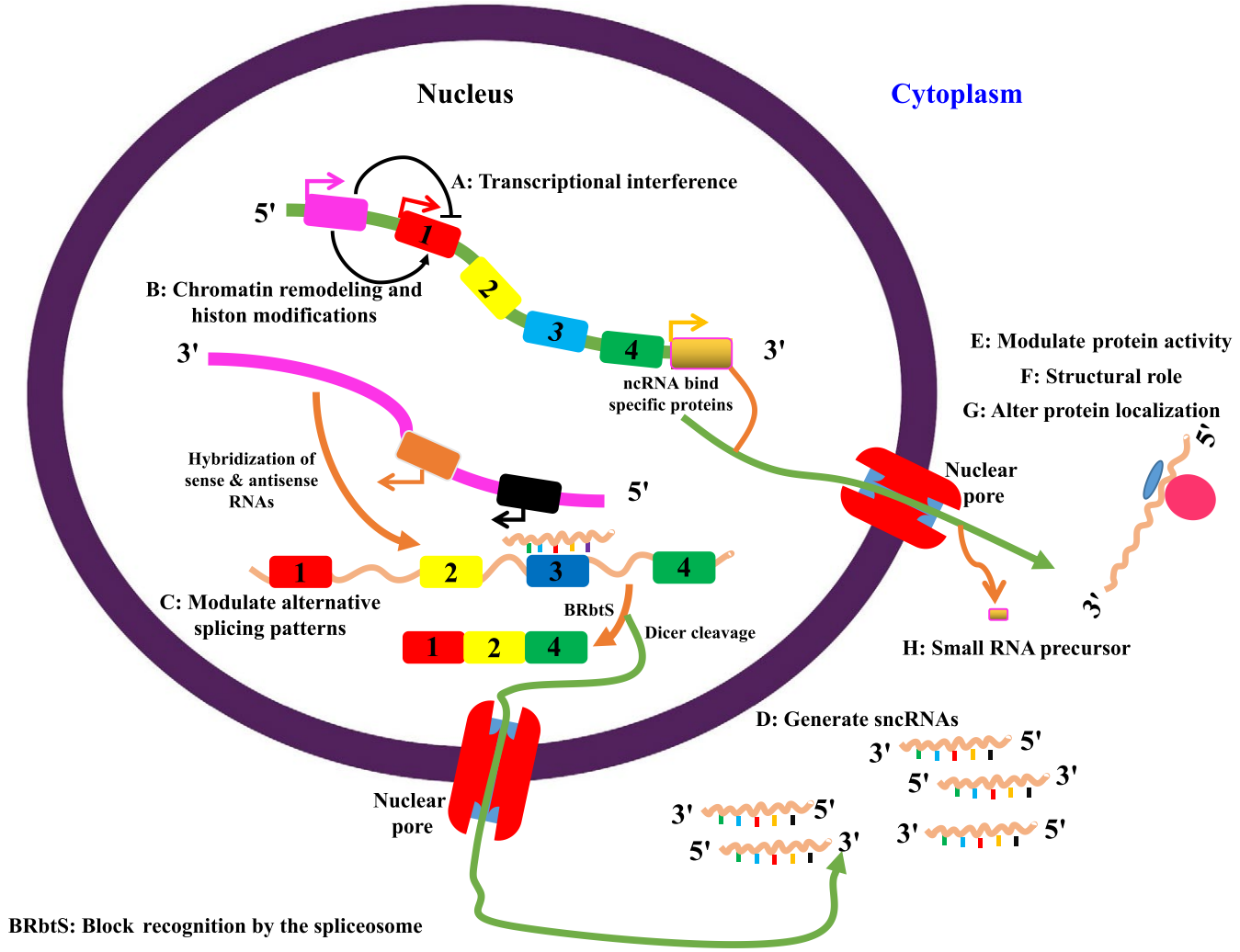

FIGURE 1 The main regulatory mechanism of lncRNAs. This figure is referred to the figure in reference [133], transcription form the upstream promoter of protein encoding gene, impact the gene expression through transcriptional interference medicated by inhibition of recruiting RNA polymerase II (A), or through B inducing chromatin remodeling and/or histone modification; (B), an antisense transcript can further hybridize to sense transcript modulate alternative splicing patterns; (C) generate various endogenous small noncoding RNAs under the action of Dicer enzyme; (D), binding to specific protein, lncRNAs can modulate the activity of protein; (E), sever as structural component that forms nucleic acid-protein complex; (F), alter the cellular localization of the protein; (G), sever as the precursor molecules of small molecules of RNA (eg, miRNA, piRNA)

extensive attention as a new type of epigenetic regulatory molecule, and evidence indicates that lncRNAs play an important role in epigenetic regulation.[42] For example, the lncRNA TARID (TCF21 antisense RNA, including demethylation) activates TCF21 expression by inducing demethylation of the TCF21 promoter. In addition to TCF21, TARID can also interact with GADD45A (growth arrest and DNA-damage-inducible, alpha). GADD45A regulates DNA demethylation by recruiting thymine-DNA-glycosylase, which activates transcriptional activity.[43,44] The lncRNAXist (X chromosome inactive specific transcript) inhibits gene expression on the inactive X chromosome by regulating methylation of target genes.[45] In another example, the lncRNAs AIR and Kcnqlotl induce histone modification through the recruitment of histone-modifying enzymes that can affect target gene expression.[46,47]

3 | LNCRNAS IN THE CENTRAL NERVOUS SYSTEM (CNS) AND BRAIN

The vertebrate CNS contains an enormous diversity of neuronal and glial cell types that differentiate and form networks through an intricate developmental program that must coordinate intrinsic and extrinsic stimuli to achieve proper form and function.[48] LncRNAs have been shown to be highly expressed within the central nervous system, particularly in the brain, where they sometimes exhibit specific spatiotemporal expression patterns.[49] Cells in the CNS show strong expression of lncRNAs, with 5458 of a total 9747 lncRNA transcripts detected in the human brain, including ~40% of the most highly and differentially expressed lncRNAs.[48,50] These lncRNAs have been shown to be involved in several key aspects

of brain development and function, such as synaptogenesis, neurogenesis, and GABAergic interneuron function. Abnormalities in these processes have been implicated in several neurodevelopmental and neurodegenerative disorders, including ASDs, epilepsy and Alzheimer's disease (Table 1).

LncRNAs are emerging as key regulators of neurogenesis. Loss-of-function studies performed in embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) have found that differentiation pathways are defective upon lncRNA knockdown,[51-53] and several lncRNAs have been identified as integral components in neurogenesis.[51,54] Among these lncRNAs, Sox2 overlapping transcript (Sox2OT) is a highly conserved lncRNA that overlaps the Sox2 gene.[55] Sox2 is a transcription factor critical in maintaining the self-renewal properties of neural stem cells and regulating the selection of germ layers in embryonic neurogenesis.[56,57] Sox2 also plays key roles in adult neurogenesis.[58] Sox2DOT, an alternatively spliced isoform of Sox2OT, is also expressed in mouse brain and is enriched in areas associated with neurogenesis.[59] A recent study has revealed that the lncRNA rhabdomyosarcoma 2-associated transcript (RMST) physically interacts with Sox2 to coregulate a large pool of downstream genes implicated in neurogenesis.[60]

Formation of functional synapses is the fundamental process required for establishing neural circuits and ultimately for expressing complex behavior. This process is characterized by increased proliferation of neuronal cells and overproduction of synaptic connections.[61,62] Aberrant regulation of synaptogenesis is more commonly seen than aberrant regulation of neurogenesis in many neurological disorders, such as ASDs and schizophrenia.[63] The lncRNA MALAT1, which has been reported to be enriched in neurons and nuclear speckles, regulates synaptic density and the expression levels of neuroligin 1 (NLGN1) and synaptic cell-adhesion molecule (SynCAM1) by regulation of serine/arginine-rich splicing factor.[38]

The critical balance between excitation and inhibition in the brain is maintained by two major classes of neurons: excitatory projection neurons and inhibitory local circuit interneurons.[64] GABA primarily mediates inhibition; thus, GABAergic interneuron function has been associated with many neurodevelopmental and neurodegenerative disorders such as ASDs, schizophrenia, and epilepsy.[65-67] Many lncRNAs, including Gtl2, Rian, Evf2, Copg2as, Dlx6-AS1 and others, have been reported to participate in the regulation of GABAergic interneuron functions.[68,69] Evf2 is transcribed from the Dlx-5/6 ultraconserved region that recruits the transcription factors DLX and MECP2, which affect Dlx-5/6 enhancer activities via both cis- and trans-mechanisms. In an Evf2 mutant, the number of GABAergic interneurons in the dentate gyrus and hippocampus were reduced, resulting in synaptic inhibition.[70] DLX6-AS1 is a key regulator of members of the DLX family of transcription factors that are involved in GABAergic neuronal differentiation. Mariani and colleagues reported that DLX6-AS1 were upregulated in cerebral organoids derived from iPSCs made from patents with ASDs.[71] A recent study has also revealed that DLX6-AS1 upregulated in cerebral organoids derived from the autism gene CHD8 knockout iPSCs.[72]

4 | LNCRNAS AND THE RISK OF ASDS

Precise regulation of lncRNAs is essential to the development, maintenance, and function of the CNS; thus, deregulation of lncRNAs may play a critical role in neurodevelopmental disorders. Many different kinds of lncRNAs have been reported to be differentially expressed in or associated with ASDs. Other types of lncRNAs have been reported to be involved in other genetic syndromes that are associated with or cause a predisposition toward ASDs, such as fragile X syndrome, Rett syndrome, Down syndrome, Angelman syndrome, and Prader-Willi syndrome.

4.1 | LncRNAs and ASDs

ASD is a clinically and etiologically heterogeneous disorder with a complex genetic architecture. In the last decade, several studies have observed aberrant expression of lncRNAs in both postmortem brain tissue and lymphoblastoid cell lines, indicating that the function of lncRNAs may be important in the etiology of these disorders. Recently, a genomewide differential expression study of lncRNAs was performed on blood specimens from 25 paired ASD controls. A total of 3929 lncRNAs were found to be differentially expressed in the peripheral leukocytes, including 2407 upregulated and 1522 downregulated. Functional pathway analysis of those lncRNAs revealed that synaptic vesicle cycling and transport were primarily involved, and 13 synaptic lncRNAs were identified as being differently expressed in ASDs. Nineteen lncRNAs were transcribed from the Hox gene, indicating that this gene may play a very important role in the developmental of ASDs. The lncRNAs SHANK2-AS and BDNF-AS, which are transcribed from the ASD susceptibility genes SHANKs and BDNF, were also differentially expressed.[73]

To date, there have been two studies in which brain tissue from ASD subjects was assessed for changes in regulatory lncRNAs.[74,75] Ziats and colleagues performed microarray profiling of over 33 000 annotated lncRNAs and 30 000 mRNA transcripts from postmortem prefrontal cortex and cerebellum tissue from autistic and control subjects. The data illustrated that 222 lncRNAs were differentially expressed between ASD cases and controls. Of those 222 lncRNAs, 82 and 143 were unique to the prefrontal cortex and the cerebellum, respectively. They also found that the number of lncRNAs differentially expressed within control brains was much greater than the number of lncRNAs differentially expressed within autistic brains (1375 lncRNAs vs 236 lncRNAs, respectively).[74] This finding is interesting in the context of imaging studies of autistic brains, which have indicated that there are fewer specialized regions in autistic brains than in the brains of healthy subjects.[76] The sample size in this study was small, giving it limited statistical power, but the exciting conclusion invites replication and expansion of these findings with a larger sample size. The other study, through postmortem genomewide transcriptome analysis to interrogate the lncRNA, splicing, and regional gene expression pattern in autism was conducted by Parikshak and colleagues.[75] They performed rRNA-depleted RNA sequencing (RNA-seq) of 251 postmortem samples of frontal and temporal cortex and cerebellum from

TABLE 1 An overview of lncRNAs implicated in neurodegenerative disorders

Disorders	LncRNA	Function	Species	References
ASDs	C210orf121 AK128400 FTHL3 LST1 Total of 121 lncRNAs	Downregulated in ASDs brain tissue, most of their function were unknown, future studies using knockdown or overexpression techniques in a relevant model system are needed	Homo sapiens	[73]
	SEC1 COAS3 SDHA PMS2L4 Total of 100 lncRNAs	Upregulated in ASDs brain tissue, most of their function were unknown, future studies using knockdown or overexpression techniques in a relevant model system are needed	Homo sapiens	[73]
	SYP-AS1 STXBP5-AS1 STX8 Total of 13 lnRNAs	Thirteen synaptic lncRNAs differentially expressed in ASD peripheral leukocytes, associated with 11 encoding genes	Homo sapiens	[72]
	SHANK2-AS	Regulation of SHANK2	Homo sapiens	[72]
	BDNF-AS	Regulation of BDNF	Homo sapiens	[72]
	MSNP1AS	Bound to MSN, decrease in MSN transcript, moesin level, neurite number, and neurite length	Homo sapiens	[76]
	DISC2	Antisense to DISC1, deletion of DISC2 was found to associate with a patient with ASDs	Homo sapiens	[77]
	HAR1	Antisense to RELN, mutation of RELE implicated in ASDs	Homo sapiens	[78]
FXS	FMR4	Antisense to FMR1, coexpressed with FMR1, regulate in cell cycle, proliferation, and apoptosis	Homo sapiens	[86]
	FMR5	Unknown, sense to FMR1	Homo sapiens	[87]
	FMR6	Unknown, antisense to FMR1	Homo sapiens	[87]
RTT	Gtl2	Function as a host gene for small RNA in mice	Mus musculus	[103]
	AK087060	Upregulated in MECP2 KO mice; AK087060 is associate with an increase in the expression levels of its host gene Arhgef26	Mus musculus	[104]
	AK081227	Upregulated in MECP2 KO mice, upregulation of AK081227 is associated with downregulation of its host gene gamma-aminobutyric acid receptor subunit rho 2 (Gabbr2)	Mus musculus	
	RNCR3	Interacts with MeCP2 mediate chromatin remodeling, influence gene expression in male mice brain	Mus musculus	[105]
PWs	116HG	Forms a subnuclear RNA could copurifies with the transcriptional activator RBBP5 and active metabolic gene, remains tethered to the site of its transcription and increases in size in postnatal neurons and during sleep	Mus musculus	[120]
	IPW	Transcribed from PWs, is a regulator of the DLK1-DIO3 region, with overexpression in PWs and parthenogenetic iPSCs resulted in downregulation of MEGs in this locus	Homo sapiens, Mus musculus	[121-123]
	H19	Unknown	Homo sapiens	[124]
	C15orf2	Show monoallelic expression in fetal brain, the role is unknown	Homo sapiens	[125]
	MKRN3-AS1	Antisense to and genomic imprinting of ZNF127	Homo sapiens	[126]

(Continues)

48 individual with ASD and 49 controls, which was known as having the largest samples. The data suggested that 60 lncRNAs were differentially expressed between ASD cases and controls, most of which have little functional annotation. Of those 60 lncRNAs, 20 have shown to interact with microRNA (miRNA)-protein complexes, and nine with FMRP (the fragile X mental retardation protein), whose mRNA targets

TABLE 1 (Continued)

Disorders	LncRNA	Function	Species	References
DS	XIST	Induces heterochromatin modification and architectural changes and then recruits polycomb-group protein transcriptionally silence the X chromosome inactive	Homo sapiens	[92-94]
	XACT	Active X chromosome specifically in human pluripotent cells	Homo sapiens	[96]
	NRON	Mediates the cytoplasmic to nuclear shuttling of the NFAT transcription factor	Homo sapiens, Mus musculus	[97,98]
AS	UBE3A-ATS	Antisense to and genomic imprinting of UBE3A	Homo sapiens, Mus musculus	[108-112]
2p15-p16.1 microdeletion	FLJ16341	In critical region with three protein-coding genes BCL11A	Homo sapiens	[133]
SZ	BDNF-AS	Coexpressed with BDNF in the brain; forms dsRNA duplexes to repress BDNF expression	Homo sapiens	[141]
	DAOA-AS1	Markers of the G72/G30 genes are associated with schizophrenia in a non-Caucasian population.	Homo sapiens	[142]
	DISC2	Regulation of DISC1 that represent an excellent candidate for susceptibility to SZ	Homo sapiens	[143]
	HAR1A	Antisense to RELN, the role is unknown in SZ	Homo sapiens	[143]
	HAR1B	Antisense to RELN, the role is unknown in SZ	Homo sapiens	[143]
	C6orf217	Mutation of C6orf217 is associated with SZ	Homo sapiens	[144]
	GOMAFU	Binds directly to the splicing factors QKI and SRSF1 and dysregulation of Gomafu leads to alternative splicing patterns that resemble those observed in SZ for the archetypal SZ-associated genes DISC1 and ERBB4	Homo sapiens, Mus musculus	[145,69]
	C6UAS	Play a regulatory role on the expression of C6orf4 that involved in SZ	Homo sapiens	[146]
AD	BACE-AS1	Upregulated in Alzheimer's brains; promotes BACE1 stability by blocking a miRNA binding site	Homo sapiens	[41,141]
	BC200	Brain-specific transcript that represses translation in dendrites to allow spatial translation regulation in postsynaptic microdomains; the role in AD is unknown	Homo sapiens, Mus musculus	[147,148]
	GDNFOS	Antisense to GDNF, the role is unknown	Homo sapiens,	[149]
	SOX2-OT	May regulate Sox2 in neurogenesis to promote neural differentiation, also has independent roles	Homo sapiens, Mus musculus	[60]

FXS, fragile X syndrome; RTT, Rett syndrome; PWs, Prader-Willi syndrome; DS, Down syndrome; AS, Angleman syndrome; SZ, schizophrenia; AD, Alzheimer disease.

are enriched in ASD risk gene. The results have shown that dysregulation of lncRNAs is an integral component of the transcriptomic signature of ASD.

Using a genomewide association study (GWAS) and bioinformatics analysis, Kerin *et al* found that thelncRNA MSNP1AS (moesin pseudogene 1, antisense) contributes to ASD risk. MSNP1AS is transcribed from the antisense strand of MSNP1 (moesin pseudogene 1), which is from the 5p14.1 chromosomal region. This region contains the single-nucleotide polymorphism (SNP) rs4307059, which was identified by the GWAS as having a strong association with ASDs.[77] MSNP1AS is 94% identical and antisense to the X chromosome transcript MSN. MSN encodes a protein (moesin) that regulates neuronal architecture and immune response. Individuals who carry the ASD-associated rs4307059 T allele have increased expression of MSNP1AS. MSNP1AS, which binds to MSN, was highly expressed in postmortem cerebral cortex samples from individuals with ASDs. This high level of expression could decrease the production of MSN transcripts, the moesin level, and the number and length of the neurites.[78] The genes DISC1 and ST7, along with their antisense transcripts DISC2 and ST7OT1-2, have also been linked with ASDs.[79,80] These studies provide a new perspective on the identity and function of lncRNAs that are associated with ASDs.

4.2 | LncRNAs and Fragile X syndrome

Fragile X syndrome, a common cause of inherited intellectual disability and ASD, is inherited via an X-linked dominant mechanism and is characterized by moderate to severe mental retardation, macroorchidism (the normal testicular volume is 20 mL, while 50% of fragile X patients had testicular volumes of 30-50 mL), and large ears and

other facial features. This syndrome is a result of the inactivation or dysfunction of FMR1 (fragile X mental retardation gene 1).[81] In most patients, the FMR1 gene is silenced by the expansion of an unstable triplet CGG repeat motif in the 5′UTR (untranslated region) that occurs in the maternal germ line. The number of CGG repeats is 5-45 in the general population. Genes with 45-200 repeats are referred to as premutation, and often experience a CGG repeat expansion mutation that gives rise to a full mutation (>200 repeats) in the offspring.[82,83] An FMR1 gene containing more than 200 repeats is transcriptionally silenced by hypermethylation of the entire promoter region and flanking areas, resulting in decreased FMRP levels in the brain.[84,85] There is much evidence indicating that the etiology of fragile X syndrome is affected by lncRNAs. FMR4 and FMR1-AS1, an antisense lncRNA that originates at the FMR1 gene locus and overlaps the CGG repeats region, are also silenced in fragile X syndrome patients but upregulated in premutation carriers.[86,87] Loss-of-function and gain-of-function experiments have shown that FMR4 regulates cell cycle, proliferation and apoptosis. In addition, when FMR4 is knocked down or overexpressed in HEK293T cells, genomewide changes in gene expression occur. In differentiating human neural precursor cells, FMR4 expression is developmentally regulated in opposition to expression of both FMR1 and MBD4.[88] These data indicate that FMR4 is a regulator of gene expression through trans-activity, independent of FMR1.[88]

Two new lncRNAs, FMR5 and FMR6, have recently been linked to fragile X syndrome.[12] FMR5 is a sense lncRNA transcribed upstream of the FMR1 promoter, while FMR6 is an antisense transcript overlapping the 3′UTR of FMR1. FMR5 is expressed similarly in several human brain regions from unaffected individuals and from full and premutation patients. However, FMR6 is silenced in individuals with a full mutation or a premutation, suggesting abnormal transcription and/or chromatin remodeling prior to transition to the full mutation. Furthermore, the expression of FMR4, FMR5, and FMR6 was found to be detectable in the majority of patient leukocyte RNA samples, suggesting that it may be feasible to use these lncRNAs as biomarkers for fragile X syndrome.

4.3 | LncRNAs and Down syndrome

Down syndrome (DS), the leading genetic cause of intellectual disabilities, is a common disorder caused by trisomy 21. Most DS patients also face multiple other health issues, such as congenital heart defects and hematopoietic disorders.[89,90] X chromosome inactivation (XCI) is essential in female mammals, and nature has evolved a mechanism to compensate for the difference in number of X-linked gene copies between females and males.[91] XIST(X-inactive specific transcript) is a conserved lncRNA that is produced exclusively from the inactive X chromosome and "paints" the interphase chromosome structure.[92] XIST induces numerous heterochromatin modifications and architectural changes and then recruits polycomb-group protein to transcriptionally silence the inactive X chromosome.[93-95] A notable recent report from Jiang and coworkers described the use of genome editing to control the expression of XIST. These researchers' method successfully silenced one copy of chromosome 21 in iPSCs derived from patients with DS,[96] resulting in improved deficiencies in proliferation and neural rosette formation. Importantly, this successful trisomy silencing in vitro overcomes a key step toward potential development of "chromosome therapy."[96] A study conducted by Celine and colleagues showed that the lncRNA XACT is expressed from and "coats" the active X chromosome in human pluripotent cells.[97] XIST and XACT display a common function of lncRNAs by inducing chromatin remodeling and histone modification to regulate the transcription of multiple genes. In addition, nonprotein-coding RNA, repressor of NFAT (NRON), which is a lncRNA that mediates shuttling of the NFAT transcription factor between the cytoplasm and the nucleus, may also be involved in DS.[98] In animal models, deregulation of the DSCR1 and DYRK1A genes, which act synergistically to prevent nuclear occupancy of NFATc transcription factors, leads to reduced NFATc activity and contributes to many features of DS. These data suggest a potential link between NRON activity and DS pathophysiology.[99,100]

4.4 | LncRNAs and Rett syndrome

Rett syndrome (RTT) is an X-linked postnatal neurological disorder of the gray matter of the brain, which almost exclusively affects females but has also been found in male patients. Typical features include a slowed rate of head growth, repetitive stereotypical hand movements, seizures, and a lack of verbal skills.[101,102] Mutations in the gene encoding methyl-CpG binding protein 2 (MeCP2) were initially reported to cause this disorder. MeCP2, which can bind to methylated-CpG dinucleotides and affect gene expression, is abundant in the neurons of the mature nervous system.[2] In a mouse model of RTT, the expression of the lncRNA Gtl2, which is homologous to MEG3 (maternally expressed gene 3) in humans, was increased.[103] Paolo and coauthors reported that the lncRNAs AK081227 and AK087060 were both upregulated in MeCP2-null mice brains. Additionally, this overexpression of AK081227 was associated with downregulation of the Gabrr2 (gamma-aminobutyric acid receptor subunit Rho 2) gene, which is the host protein-coding gene of AK081227.[104] Scott *et al* revealed that the lncRNA RNCR3 interacts with MeCP2 to mediate chromatin remodeling, influencing gene expression in the male mouse brain.[105] All of these findings supply either indirect or direct evidence that lncRNA dysfunction has the potential to contribute to the etiology of RTT.

4.5 | LncRNAs, Angelman syndrome, and Prader-Willi syndrome

Angelman syndrome (AS) is a neurodevelopmental disorder characterized by severe intellectual or developmental disability, sleep disturbance, seizures, jerky movements and an abnormal demeanor.[106] The loss of maternal genetic material at the 15q11.2-13 locus results in AS.[107] The dosage of an imprinted gene or genes within the duplicated region underlies the autism risk in these individuals. Ubiquitin protein ligase E3A (UBE3A) is the only gene within the 15q11-13 duplicated segment, and a disruption in the UBE3A gene is thought to be causative for AS.[108] The lncRNA UBE3A-ATS, which can regulate the expression of UBE3A, is transcribed antisense to UBE3A,[109,110] and

high expression of UBE3A-ATS is detected in AS patients and mouse models.[111,112] Additionally, many studies have demonstrated that reduction of UBE3A-ATS levels and sustained unsilencing of paternal UBE3A may be a feasible therapy for AS.[113,114] However, some contrary results showed that unsilencing of UB3EA may also occur when UB3E-ATS is not present, suggesting that the regulation of UB3EA is more complex and is not limited to silencing by UB3E-ATS.[115,116]

Prader-Willi syndrome (PWS) is characterized by hypotonia, short stature, developmental delays, intellectual disability and behavioral issues, including ASDs.[117] PWS is caused by the deletion or lack of expression of genes in the15q11.2-q13 region of the paternally inherited chromosome. In most PWS patients, approximately 20 paternally inherited genes are missing.[118,119] The lncRNA 116HG has also been reported to participate in the development of PWS. 116HG is a subnuclear RNA that copurifies with the transcriptional activator RBBP5 and an active metabolic gene, remains tethered to the site of its transcription and increases in size in postnatal neurons and during sleep. A mouse model lacking 116HG exhibits increased energy expenditure corresponding to the dysregulation of diurnally expressed mammalian target of rapamycin (mTOR) and the circadian genes Clock, cryptochrome circadian clock1 (Cry1) and period circadian clock 2 (Per2).[120] Another lncRNA, IPW, which is transcribed from the 15.q11.2-q13 region of the chromosome is a regulator of the delta-like 1 homolog-deiodinase 3 (DLK1-DIO3) regions. Overexpression of IPW in subjects with PWS and in parthenogenetic iPSCs resulted in downregulation of MEGs in this locus. Of note, the gene changes are due to chromatin modifications, rather than DNA methylation.[121-123] Moreover, a series of investigations have also demonstrated that the lncRNAs H19, C15orf2, MKRN3-AS1, and UBE3A-AS1 may be implicated in the development of PWS.[124-127]

4.6 | LncRNAs and other neurodevelopmental disorders that is associated with autistic traits

In the last decade, some rare neurodevelopmental disorders have been reported. Phelan-McDermid syndrome (PMS) is characterized by global developmental delays, intellectual disability, absent or delayed speech, hypotonia, and ASD or ASD features.[128] The deletion of the human SHANK3 gene near the terminus of chromosome 22q13 has been confirmed to result in this syndrome. Phosphatase and tensin homolog on chromosome 10 (PTEN) hamartoma tumor syndrome (PHTS) is the term used to encompass the range of symptoms identified as being caused by PTEN mutations. These symptoms include mental retardation, developmental delay and ASD.[129,130] 2p15-p16.1 microdeletion syndrome is characterized by mental retardation, autistic features, short stature and various dysmorphic facial features.[131] The genetic cause of this disorder is not entirely clear, but candidate genes include PTEN, SHANK3, calcium voltage-gated channel subunit alpha1 C (CACNA1C),[132] B-cell CLL/lymphoma 11A (BCL11A), poly(A) polymerase gamma (PAPOLG) and REL proto-oncogene (REL). One lncRNA gene, FLJ16341, may also be implicated in 2p15-p16.1 microdeletion syndrome, but the function of this lncRNA is still unclear.[133,134]

5 | CONCLUSIONS

With the completion of the human genome project, the primary challenge facing the life sciences is to determine the function of genes and their regulatory networks. The discovery of functional roles of lncRNAs not only provides a new pathway for researching the growth and development of organisms but also provides a prospect for the development of tissue engineering technology and novel targeted gene therapy technology. LncRNAs are important to the CNS because they play roles in maintenance of pluripotency, cell fate, neurogenesis and migration, synaptogenesis, neuron-specific relaxation of epigenetic imprinting, repression of neural genes in nonneural cells, and brain tissue patterning.[135] Because long-term memory formation is based on the alteration of chromatin structure, lncRNAs are even involved in memory.[136,137] The involvement of lncRNAs in neurodevelopmental and neurodegenerative disorders and other neurological diseases further illustrates their important role in CNS development and function. However, research on lncRNAs, especially in CNS development and neurological disorders, is still in its initial stages.[138] We suggest that productive directions for future studies may include: (i) determining the novel and higher order functions that are modulated by lncRNA-mediated mechanisms; (ii) elucidating the specific spatial and temporal expression patterns of lncRNAs and fully illustrating the dynamics of lncRNAs in the development of the CNS system and in neurological disorders; and (iii) studying how lncRNAs modulate pathogenetic events in neurodevelopmental disorders. Additionally, lncRNA research should not be limited to animal or cellular models.[139] More insight into their roles in ASD and other neurodevelopmental disorders might require the incorporation of epidemiological studies carried out on patients, as well as improvements in bioinformatics,[140] which will help in understanding the function of those lncRNAs that have not been well characterized.

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COMPETING INTERESTS

The authors have declared that no competing interests exist.

REFERENCES

1. American Psychiatric Association DSM-Task Force Arlington VA US. *Diagnostic and Statistical Manual of Mental Disorders: Dsm-5™*, 5th edn, Vol. 57. Washington, D.C.: American Psychiatric Publishing; 2013:207.
2. Ornoy A, Weinstein-Fudim L, Ergaz Z. Genetic syndromes, maternal diseases and antenatal factors associated with autism spectrum disorders (ASD). *Front Neurosci*. 2016;10:316.
3. Christensen DL, Baio J, Van Naarden Braun K, et al. Prevalence and characteristics of autism spectrum disorder among children aged 8 years-autism and developmental disabilities monitoring

network, 11 sites, United States, 2012. *MMWR Surveill Summ*. 2016;65:1-23.
4. Kim YS, Leventhal BL, Koh YJ, et al. Prevalence of autism spectrum disorders in a total population sample. *Am J Psychiatry*. 2011;168:904-912.
5. Wan Y, Hu Q, Li T, et al. Prevalence of autism spectrum disorders among children in china: a systematic review. *Shanghai Arch Psychiatry*. 2013;25:70-80.
6. Abrahams BS, Geschwind DH. Advances in autism genetics: on the threshold of a new neurobiology. *Nat Rev Genet*. 2008;9:341-355.
7. Anney R, Klei L, Pinto D, et al. A genome-wide scan for common alleles affecting risk for autism. *Hum Mol Genet*. 2010;19:4072-4082.
8. Jiang HY, Xu LL, Shao L, et al. Maternal infection during pregnancy and risk of autism spectrum disorders: a systematic review and meta-analysis. *Brain Behav Immun*. 2016;58:165-172.
9. Mostafa GA, Bjørklund G, Urbina MA, et al. The levels of blood mercury and inflammatory-related neuropeptides in the serum are correlated in children with autism spectrum disorder. *Metab Brain Dis*. 2016;31:593-599.
10. Prandini P, Pasquali A, Malerba G, et al. The association of rs4307059 and rs35678 markers with autism spectrum disorders is replicated in italian families. *Psychiatr Genet*. 2012;22:177-181.
11. Wang Y, Fang Y, Zhang F, et al. Hypermethylation of the enolase gene (eno2) in autism. *Eur J Pediatr*. 2014;173:1233-1244.
12. Pastori C, Peschansky VJ, Barbouth D, et al. Comprehensive analysis of the transcriptional landscape of the human fmr1 gene reveals two new long noncoding rnas differentially expressed in fragile x syndrome and fragile x-associated tremor/ataxia syndrome. *Hum Genet*. 2014;133:59-67.
13. Choi SY, Pang K, Kim JY, et al. Post-transcriptional regulation of shank3 expression by microRNAs related to multiple neuropsychiatric disorders. *Mol Brain*. 2015;8:74.
14. Geaghan M, Cairns MJ. MicroRNA and posttranscriptional dysregulation in psychiatry. *Biol Psychiatry*. 2015;78:231-239.
15. Kichukova TM, Popov NT, Ivanov HY, et al. Circulating microRNAs as a novel class of potential diagnostic biomarkers in neuropsychiatric disorders. *Folia Med (Plovdiv)*. 2015;57:159-172.
16. Mor M, Nardone S, Sams DS, et al. Hypomethylation of mir-142 promoter and upregulation of microRNAs that target the oxytocin receptor gene in the autism prefrontal cortex. *Mol Autism*. 2015;6:46.
17. Stamova B, Ander BP, Barger N, et al. Specific regional and age-related small noncoding rna expression patterns within superior temporal gyrus of typical human brains are less distinct in autism brains. *J Child Neurol*. 2015;30:1930-1946.
18. Zhao D, Lin M, Chen J, et al. MicroRNA profiling of neurons generated using induced pluripotent stem cells derived from patients with schizophrenia and schizoaffective disorder, and 22q11.2 del. *PLoS ONE*. 2015;10:e0132387.
19. Hicks SD, Ignacio C, Gentile K, et al. Salivary miRNA profiles identify children with autism spectrum disorder, correlate with adaptive behavior, and implicate ASD candidate genes involved in neurodevelopment. *BMC Pediatr*. 2016;16:52.
20. Panjwani N, Wilson MD, Addis L, et al. A microRNA-328 binding site in pax6 is associated with centrotemporal spikes of rolandic epilepsy. *Ann Clin Transl Neurol*. 2016;3:512-522.
21. Nagano T, Fraser P. No-nonsense functions for long noncoding RNAs. *Cell*. 2011;145:178-181.
22. Rinn JL, Chang HY. Genome regulation by long noncoding RNAs. *Annu Rev Biochem*. 2012;81:145-166.
23. Ponting CP, Oliver PL, Reik W. Evolution and functions of long noncoding RNAs. *Cell*. 2009;136:629-641.
24. Taft RJ, Pang KC, Mercer TR, et al. Non-coding RNAs: regulators of disease. *J Pathol*. 2010;220:126-139.
25. Wapinski O, Chang HY. Long noncoding RNAs and human disease. *Trends Cell Biol*. 2011;21:354-361.
26. Kaikkonen MU, Lam MT, Glass CK. Non-coding RNAs as regulators of gene expression and epigenetics. *Cardiovasc Res*. 2011;90:430-440.
27. Zhu S, Zhang XO, Yang L. Panning for long noncoding RNAs. *Biomolecules*. 2013;3:226-241.
28. Xia T, Xiao BX, Guo JM. Acting mechanisms and research methods of long noncoding RNAs. *Yi Chuan*. 2013;35:269-280.
29. Li H, Zhu H, Ge J. Long noncoding RNA: recent updates in atherosclerosis. *Int J Biol Sci*. 2016;12:898-910.
30. Guttman M, Rinn JL. Modular regulatory principles of large noncoding RNAs. *Nature*. 2012;482:339-346.
31. Feng J, Bi C, Clark BS, et al. The evf-2 noncoding RNA is transcribed from the dlx-5/6 ultraconserved region and functions as a dlx-2 transcriptional coactivator. *Genes Dev*. 2006;20:1470-1484.
32. Ohno M, Fukagawa T, Lee JS, et al. Triplex-forming dnas in the human interphase nucleus visualized in situ by polypurine/polypyrimidine DNA probes and antitriplex antibodies. *Chromosoma*. 2002;111:201-213.
33. Crampton N, Bonass WA, Kirkham J, et al. Collision events between RNA polymerases in convergent transcription studied by atomic force microscopy. *Nucleic Acids Res*. 2006;34:5416-5425.
34. Pagano A, Castelnuovo M, Tortelli F, et al. New small nuclear RNA gene-like transcriptional units as sources of regulatory transcripts. *PLoS Genet*. 2007;3:e1.
35. Annilo T, Kepp K, Laan M. Natural antisense transcript of natriuretic peptide precursor a (NPPA): structural organization and modulation of NPPA expression. *BMC Mol Biol*. 2009;10:81.
36. Tay Y, Rinn J, Pandolfi PP. The multilayered complexity of ceRNA crosstalk and competition. *Nature* 2014;505:344-352.
37. Jolly C, Lakhotia SC. Human sat III and drosophila hsr omega transcripts: a common paradigm for regulation of nuclear RNA processing in stressed cells. *Nucleic Acids Res*. 2006;34:5508-5514.
38. Tripathi V, Ellis JD, Shen Z, et al. The nuclear-retained noncoding RNA MALAT1 regulates alternative splicing by modulating SR splicing factor phosphorylation. *Mol Cell*. 2010;39:925-938.
39. Bernard D, Prasanth KV, Tripathi V, et al. A long nuclear-retained non-coding RNA regulates synaptogenesis by modulating gene expression. *EMBO J*. 2010;29:3082-3093.
40. Faghihi MA, Modarresi F, Khalil AM, et al. Expression of a noncoding RNA is elevated in Alzheimer's disease and drives rapid feed-forward regulation of beta-secretase. *Nat Med*. 2008;14:723-730.
41. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*. 2002;297:353-356.
42. Rinn JL. LncRNAs: linking RNA to chromatin. *Cold Spring Harb Perspect Biol*. 2014;6:a018614.
43. Liu Z, Wang Z, Li Y, et al. Association of genomic instability, and the methylation status of imprinted genes and mismatch-repair genes, with neural tube defects. *Eur J Hum Genet*. 2012;20:516-520.
44. Arab K, Park YJ, Lindroth AM, et al. Long noncoding RNA TARID directs demethylation and activation of the tumor suppressor TCF21 via GADD45A. *Mol Cell*. 2014;55:604-614.
45. Wutz A, Gribnau J. X inactivation Xplained. *Curr Opin Genet Dev*. 2007;17:387-393.
46. Nagano T, Mitchell JA, Sanz LA, et al. The air noncoding RNA epigenetically silences transcription by targeting G9a to chromatin. *Science*. 2008;322:1717-1720.
47. Redrup L, Branco MR, Perdeaux ER, et al. The long noncoding RNA Kcnq1ot1 organises a lineage-specific nuclear domain for epigenetic gene silencing. *Development*. 2009;136:525-530.
48. Knauss JL, Sun T. Regulatory mechanisms of long noncoding RNAs in vertebrate central nervous system development and function. *Neuroscience*. 2013;235:200-214.
49. Lipovich L, Tarca AL, Cai J, et al. Developmental changes in the transcriptome of human cerebral cortex tissue: long noncoding RNA transcripts. *Cereb Cortex*. 2014;24:1451-1459.

50. Derrien T, Johnson R, Bussotti G, et al. The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. *Genome Res*. 2012;22:1775-1789.
51. Ng SY, Johnson R, Stanton LW. Human long non-coding rnas promote pluripotency and neuronal differentiation by association with chromatin modifiers and transcription factors. *EMBO J*. 2012;31:522-533.
52. Klattenhoff CA, Scheuermann JC, Surface LE, et al. Braveheart, a long noncoding RNA required for cardiovascular lineage commitment. *Cell*. 2013;152:570-583.
53. Sun L, Goff LA, Trapnell C, et al. Long noncoding rnas regulate adipogenesis. *Proc Natl Acad Sci USA*. 2013;110:3387-3392.
54. Lin M, Pedrosa E, Shah A, et al. RNA-seq of human neurons derived from iPS cells reveals candidate long non-coding RNAs involved in neurogenesis and neuropsychiatric disorders. *PLoS ONE*. 2011;6:e23356.
55. Fantes J, Ragge NK, Lynch SA, et al. Mutations in SOX2 cause anophthalmia. *Nat Genet*. 2003;33:461-463.
56. Mizuseki K, Kishi M, Matsui M, et al. Xenopus Zic-related-1 and Sox-2, two factors induced by chordin, have distinct activities in the initiation of neural induction. *Development*. 1998;125:579-587.
57. Thomson M, Liu SJ, Zou LN, et al. Pluripotency factors in embryonic stem cells regulate differentiation into germ layers. *Cell*. 2011;145:875-889.
58. Favaro R, Valotta M, Ferri AL, et al. Hippocampal development and neural stem cell maintenance require Sox2-dependent regulation of Shh. *Nat Neurosci*. 2009;12:1248-1256.
59. Amaral PP, Neyt C, Wilkins SJ, et al. Complex architecture and regulated expression of the Sox2ot locus during vertebrate development. *RNA*. 2009;15:2013-2027.
60. Ng SY, Bogu GK, Soh BS, et al. The long noncoding RNA RMST interacts with SOX2 to regulate neurogenesis. *Mol Cell*. 2013;51:349-359.
61. Petanjek Z, Judas M, Simic G, et al. Extraordinary neoteny of synaptic spines in the human prefrontal cortex. *Proc Natl Acad Sci USA*. 2011;108:13281-13286.
62. Hong JH, Park M. Understanding synaptogenesis and functional connectome in C. elegans by imaging technology. *Front Synaptic Neurosci* 2016;8:18.
63. Grant SG. Synaptopathies: diseases of the synaptome. *Curr Opin Neurobiol*. 2012;22:522-529.
64. Bond AM, Vangompel MJ, Sametsky EA, et al. Balanced gene regulation by an embryonic brain ncRNA is critical for adult hippocampal GABA circuitry. *Nat Neurosci*. 2009;12:1020-1027.
65. Stansfield KH, Ruby KN, Soares BD, et al. Early-life lead exposure recapitulates the selective loss of parvalbumin-positive GABAergic interneurons and subcortical dopamine system hyperactivity present in schizophrenia. *Transl Psychiatry*. 2015;5:e522.
66. Baek H, Yi MH, Pandit S, et al. Altered expression of KCC2 in GABAergic interneuron contributes prenatal stress-induced epileptic spasms in infant rat. *Neurochem Int*. 2016;97:57-64.
67. Hashemi E, Ariza J, Rogers H, et al. The number of parvalbumin-expressing interneurons is decreased in the medial prefrontal cortex in autism. *Cereb Cortex*. 2017;17:1931-1943.
68. Mercer TR, Dinger ME, Sunkin SM, et al. Specific expression of long noncoding RNAs in the mouse brain. *Proc Natl Acad Sci USA*. 2008;105:716-721.
69. Mercer TR, Qureshi IA, Gokhan S, et al. Long noncoding RNAs in neuronal-glial fate specification and oligodendrocyte lineage maturation. *BMC Neurosci*. 2010;11:14.
70. Cobos I, Calcagnotto ME, Vilaythong AJ, et al. Mice lacking Dlx1 show subtype-specific loss of interneurons, reduced inhibition and epilepsy. *Nat Neurosci*. 2005;8:1059-1068.
71. Mariani J, Coppola G, Zhang P, et al. FOXG1-dependent dysregulation of GABA/glutamate neuron differentiation in autism spectrum disorders. *Cell*. 2015;162:375-390.
72. Wang P, Mokhtari R, Pedrosa E, et al. CRISPR/Cas9-mediated heterozygous knockout of the autism gene CHD8 and characterization of its transcriptional networks in cerebral organoids derived from iPS cells. *Molecular Autism*. 2017;8:11.
73. Wang Y, Zhao X, Ju W, et al. Genome-wide differential expression of synaptic long noncoding RNAs in autism spectrum disorder. *Transl Psychiatry*. 2015;5:e660.
74. Ziats MN, Rennert OM. Aberrant expression of long noncoding RNAs in autistic brain. *J Mol Neurosci*. 2013;49:589-593.
75. Parikshak NN, Swarup V, Belgard TG, et al. Genome-wide changes in lncRNA, splicing, and regional gene expression patterns in autism. *Nature*. 2016;540:423-427.
76. Minshew NJ, Keller TA. The nature of brain dysfunction in autism: functional brain imaging studies. *Curr Opin Neurol*. 2010;23:124-130.
77. Wang K, Zhang H, Ma D, et al. Common genetic variants on 5p14.1 associate with autism spectrum disorders. *Nature*. 2009;459:528-533.
78. Kerin T, Ramanathan A, Rivas K, et al. A noncoding RNA antisense to moesin at 5p14.1 in autism. *Sci Transl Med* 2012;4:128ra140.
79. Williams JM, Beck TF, Pearson DM, et al. A 1q42 deletion involving DISC1, DISC2, and TSNAX in an autism spectrum disorder. *Am J Med Genet A*. 2009;149A:1758-1762.
80. Vincent JB, Petek E, Thevarkunnel S, et al. The RAY1/ST7 tumor-suppressor locus on chromosome 7q31 represents a complex multi-transcript system. *Genomics* 2002;80:283-294.
81. Verkerk AJ, Pieretti M, Sutcliffe JS, et al. Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. *Cell*. 1991;65:905-914.
82. Fu YH, Kuhl DP, Pizzuti A, et al. Variation of the CGG repeat at the fragile X site results in genetic instability: resolution of the Sherman paradox. *Cell*. 1991;67:1047-1058.
83. Heitz D, Devys D, Imbert G, et al. Inheritance of the fragile X syndrome: size of the fragile X premutation is a major determinant of the transition to full mutation. *J Med Genet*. 1992;29:794-801.
84. Pieretti M, Zhang FP, Fu YH, et al. Absence of expression of the FMR-1 gene in fragile X syndrome. *Cell*. 1991;66:817-822.
85. Verheij C, Bakker CE, de Graaff E, et al. Characterization and localization of the FMR-1 gene product associated with fragile X syndrome. *Nature*. 1993;363:722-724.
86. Ladd PD, Smith LE, Rabaia NA, et al. An antisense transcript spanning the CGG repeat region of FMR1 is upregulated in premutation carriers but silenced in full mutation individuals. *Hum Mol Genet*. 2007;16:3174-3187.
87. Khalil AM, Faghihi MA, Modarresi F, et al. A novel RNA transcript with antiapoptotic function is silenced in fragile X syndrome. *PLoS ONE*. 2008;3:e1486.
88. Peschansky VJ, Pastori C, Zeier Z, et al. Changes in expression of the long non-coding RNA FMR4 associate with altered gene expression during differentiation of human neural precursor cells. *Front Genet*. 2015;6:263.
89. Megarbane A, Ravel A, Mircher C, et al. The 50th anniversary of the discovery of trisomy 21: the past, present, and future of research and treatment of down syndrome. *Genet Med*. 2009;11:611-616.
90. Gardiner KJ. Molecular basis of pharmacotherapies for cognition in Down syndrome. *Trends Pharmacol Sci*. 2010;31:66-73.
91. Brown CJ, Hendrich BD, Rupert JL, et al. The human XIST gene: analysis of a 17 kb inactive X-specific RNA that contains conserved repeats and is highly localized within the nucleus. *Cell*. 1992;71:527-542.
92. Clemson CM, McNeil JA, Willard HF, et al. XIST RNA paints the inactive X chromosome at interphase: evidence for a novel RNA involved in nuclear/chromosome structure. *J Cell Biol*. 1996;132:259-275.

93. Plath K, Fang J, Mlynarczyk-Evans SK, et al. Role of histone H3 lysine 27 methylation in X inactivation. *Science*. 2003;300:131-135.
94. Heard E. Delving into the diversity of facultative heterochromatin: the epigenetics of the inactive X chromosome. *Curr Opin Genet Dev*. 2005;15:482-489.
95. Hall LL, Lawrence JB. XIST RNA and architecture of the inactive X chromosome: implications for the repeat genome. *Cold Spring Harb Symp Quant Biol*. 2010;75:345-356.
96. Jiang J, Jing Y, Cost GJ, et al. Translating dosage compensation to trisomy 21. *Nature*. 2013;500:296-300.
97. Vallot C, Huret C, Lesecque Y, et al. XACT, a long noncoding transcript coating the active X chromosome in human pluripotent cells. *Nat Genet*. 2013;45:239-241.
98. Willingham AT, Orth AP, Batalov S, et al. A strategy for probing the function of noncoding RNAs finds a repressor of NFAT. *Science*. 2005;309:1570-1573.
99. Arron JR, Winslow MM, Polleri A, et al. NFAT dysregulation by increased dosage of DSCR1 and DYRK1A on chromosome 21. *Nature*. 2006;441:595-600.
100. de la Luna S, Estivill X. Cooperation to amplify gene-dosage-imbalance effects. *Trends Mol Med*. 2006;12:451-454.
101. Jian L, Nagarajan L, de Klerk N, et al. Predictors of seizure onset in Rett syndrome. *J Pediatr*. 2006;149:542-547.
102. Moss J, Howlin P. Autism spectrum disorders in genetic syndromes: implications for diagnosis, intervention and understanding the wider autism spectrum disorder population. *J Intellect Disabil Res*. 2009;53:852-873.
103. Jordan C, Li HH, Kwan HC, et al. Cerebellar gene expression profiles of mouse models for Rett syndrome reveal novel MeCP2 targets. *BMC Med Genet*. 2007;8:36.
104. Petazzi P, Sandoval J, Szczesna K, et al. Dysregulation of the long non-coding RNA transcriptome in a Rett syndrome mouse model. *RNA Biol*. 2013;10:1197-1203.
105. Maxwell SS, Pelka GJ, Tam PP, et al. Chromatin context and ncRNA highlight targets of MeCP2 in brain. *RNA Biol*. 2013;10:1741-1757.
106. Wink LK, Fitzpatrick S, Shaffer R, et al. The neurobehavioral and molecular phenotype of Angelman syndrome. *Am J Med Genet A*. 2015;167A:2623-2628.
107. LaSalle JM, Reiter LT, Chamberlain SJ. Epigenetic regulation of UBE3A and roles in human neurodevelopmental disorders. *Epigenomics*. 2015;7:1213-1228.
108. Matsuura T, Sutcliffe JS, Fang P, et al. De novo truncating mutations in E6-AP ubiquitin-protein ligase gene (UBE3A) in Angelman syndrome. *Nat Genet*. 1997;15:74-77.
109. Chamberlain SJ, Brannan CI. The prader-willi syndrome imprinting center activates the paternally expressed murine Ube3a antisense transcript but represses paternal Ube3a. *Genomics*. 2001;73:316-322.
110. Johnstone KA, DuBose AJ, Futtner CR, et al. A human imprinting centre demonstrates conserved acquisition but diverged maintenance of imprinting in a mouse model for Angelman syndrome imprinting defects. *Hum Mol Genet*. 2006;15:393-404.
111. Rougeulle C, Cardoso C, Fontes M, et al. An imprinted antisense RNA overlaps UBE3A and a second maternally expressed transcript. *Nat Genet*. 1998;19:15-16.
112. Meng L, Person RE, Beaudet AL. Ube3a-ats is an atypical RNA polymerase II transcript that represses the paternal expression of Ube3a. *Hum Mol Genet*. 2012;21:3001-3012.
113. Meng L, Person RE, Huang W, et al. Truncation of Ube3a-ATS unsilences paternal Ube3a and ameliorates behavioral defects in the Angelman syndrome mouse model. *PLoS Genet*. 2013;9:e1004039.
114. Meng L, Ward AJ, Chun S, et al. Towards a therapy for Angelman syndrome by targeting a long non-coding RNA. *Nature*. 2015;518:409-412.
115. Le Meur E, Watrin F, Landers M, et al. Dynamic developmental regulation of the large non-coding RNA associated with the mouse 7C imprinted chromosomal region. *Dev Biol*. 2005;286:587-600.
116. Huang HS, Allen JA, Mabb AM, et al. Topoisomerase inhibitors unsilence the dormant allele of Ube3a in neurons. *Nature*. 2012;481:185-189.
117. Kalsner L, Chamberlain SJ. Prader-willi, Angelman, and 15q11-q13 duplication syndromes. *Pediatr Clin North Am*. 2015;62:587-606.
118. Duker AL, Ballif BC, Bawle EV, et al. Paternally inherited microdeletion at 15q11.2 confirms a significant role for the SNORD116 C/D box snoRNA cluster in Prader-Willi syndrome. *Eur J Hum Genet*. 2010;18:1196-1201.
119. Bieth E, Eddiry S, Gaston V, et al. Highly restricted deletion of the SNORD116 region is implicated in Prader-Willi syndrome. *Eur J Hum Genet*. 2015;23:252-255.
120. Powell WT, Coulson RL, Crary FK, et al. A Prader-Willi locus lncRNA cloud modulates diurnal genes and energy expenditure. *Hum Mol Genet*. 2013;22:4318-4328.
121. Wevrick R, Kerns JA, Francke U. Identification of a novel paternally expressed gene in the Prader-Willi syndrome region. *Hum Mol Genet*. 1994;3:1877-1882.
122. Wevrick R, Francke U. An imprinted mouse transcript homologous to the human imprinted in Prader-Willi syndrome (IPW) gene. *Hum Mol Genet*. 1997;6:325-332.
123. Stelzer Y, Sagi I, Yanuka O, et al. The noncoding RNA IPW regulates the imprinted DLK1-DIO3 locus in an induced pluripotent stem cell model of Prader-Willi syndrome. *Nat Genet*. 2014;46:551-557.
124. Shi X, Sun M, Liu H, et al. Long non-coding RNAs: a new frontier in the study of human diseases. *Cancer Lett*. 2013;339:159-166.
125. Buiting K, Nazlican H, Galetzka D, et al. C15orf2 and a novel noncoding transcript from the Prader-Willi/Angelman syndrome region show monoallelic expression in fetal brain. *Genomics*. 2007;89:588-595.
126. Jong MT, Gray TA, Ji Y, et al. A novel imprinted gene, encoding a RING zinc-finger protein, and overlapping antisense transcript in the Prader-Willi syndrome critical region. *Hum Mol Genet*. 1999;8:783-793.
127. Perez P, Jang SI, Alevizos I. Emerging landscape of non-coding RNAs in oral health and disease. *Oral Dis*. 2014;20:226-235.
128. Phelan K, McDermid HE. The 22q13.3 Deletion syndrome (Phelan-McDermid syndrome). *Mol Syndromol* 2012;2:186-201.
129. McBride KL, Varga EA, Pastore MT, et al. Confirmation study of PTEN mutations among individuals with autism or developmental delays/mental retardation and macrocephaly. *Autism Res*. 2010;3:137-141.
130. Leslie NR, Longy M. Inherited PTEN mutations and the prediction of phenotype. *Semin Cell Dev Biol*. 2016;52:30-38.
131. Rajcan-Separovic E, Harvard C, Liu X, et al. Clinical and molecular cytogenetic characterisation of a newly recognised microdeletion syndrome involving 2p15-16.1. *J Med Genet*. 2007;44:269-276.
132. Li J, Zhao L, You Y, et al. Schizophrenia related variants in CACNA1C also confer risk of autism. *PLoS ONE*. 2015;10:e0133247.
133. van de Vondervoort II, Gordebeke PM, Khoshab N, et al. Long non-coding RNAs in neurodevelopmental disorders. *Front Mol Neurosci*. 2013;6:53.
134. Hu G, Zhou X, Wang Y, et al. Advances of differentiation of neural stem cells regulated by long non-coding RNAs. *J Shanghai Jiaotong Univ*. 2014;34:1087-1091.
135. Roberts TC, Morris KV, Wood MJ. The role of long non-coding RNAs in neurodevelopment, brain function and neurological disease. *Philos Trans R Soc Lond B Biol Sci*. 2014;369.
136. Swank MW, Sweatt JD. Increased histone acetyltransferase and lysine acetyltransferase activity and biphasic activation of the ERK/RSK cascade in insular cortex during novel taste learning. *J Neurosci*. 2001;21:3383-3391.
137. Egan MF, Kojima M, Callicott JH, et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*. 2003;112:257-269.

138. Alberini CM, Kandel ER. The regulation of transcription in memory consolidation. *Cold Spring Harb Perspect Biol*. 2015;7:a021741.
139. Laufer BI, Mantha K, Kleiber ML, et al. Long-lasting alterations to DNA methylation and ncRNAs could underlie the effects of fetal alcohol exposure in mice. *Dis Model Mech*. 2013;6:977-992.
140. Luo H, Bu D, Sun L, et al. Identification and function annotation of long intervening noncoding RNAs. *Brief Bioinform*. 2016;1-9.
141. Ng SY, Lin L, Soh BS, et al. Long noncoding RNAs in development and disease of the central nervous system. *Trend Genet*. 2013;29:461-468.
142. Wang X, He G, Gu N, et al. Association of G72/G30 with schizophrenia in the Chinese population. *Biochem Biophys Res Commun*. 2004;319:1281-1286.
143. Harries LW. Long non-coding RNAs and human disease. *Biechem Soc Trans*. 2012;40:902-906.
144. Amann-Zalcenstein D, Avidan N, Kanyas K, et al. AHI1, a pivotal neurodevelopmental gene, and C6orf217 are associated with susceptibility to schizophrenia. *Eur J Hum Genet*. 2006;14:1111-1119.
145. Barry G, Briggs JA, Vanichkina DP, et al. The long non-coding RNA Gomafu is acutely regulated in response to neuronal activation and involved in schizophrenia-associated alternative splicing. *Mol Psychiatry*. 2014;19:486-494.
146. Morelli C, Magnanini C, Mungall AJ, et al. Cloning and characterization of two overlapping genes in a subregion at 6q21 involved in replicative senescence and schizophrenia. *Gene*. 2000;252:217-225.
147. Qureshi IA, Mattick JS, Mehler MF. Long non-coding RNAs in nervous system function and disease. *Brain Res*. 2010;1338:20-35.
148. Mus E, Hof PR, Tiedge H. Dendritic BC200 RNA in aging and in Alzheimer's disease. *Proc Natl Acad Sci USA*. 2007;104:10679-10684.
149. Airavaara M, Pletbikova O, Doyle ME, et al. Identification of novel GDNF isoforms and cis-antisense GDNFOS gene and their regulation in human middle temporal gyrus of Alzheimer disease. *J Biol Chem*. 2011;286:45093-45102.

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